Optimal temperature and concentration profiles in a cascade of CSTR's performing Michaelis-Menten reactions with first order enzyme deactivation

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Abstract. A necessary condition is found for the intermediate temperatures and substrate concentrations in a series of CSTR's performing an enzyme-catalyzed reaction which leads to the minimum overall volume of the cascade for given initial and final temperatures and substrate concentrations. The reaction is assumed to occur in a single phase under steady state conditions. The common case of Michaelis-Menten kinetics coupled with first order deactivation of the enzyme is considered. This analysis shows that intermediate stream temperatures play as important a role as intermediate substrate concentrations when optimizing in the presence of nonisothermal conditions. The general procedure is applied to a practical example involving a series of two reactors with reasonable values for the relevant five operating parameters. These parameters are defined as dimensionless ratios involving activation energies (or enthalpy changes of reaction), preexponential factors, and initial temperature and substrate concentration. For negligible rate of deactivation, the optimality condition corresponds to having the ratio of any two consecutive concentrations as a single-parameter increasing function of the previous ratio of consecutive concentrations.

List of symbols

$C_{E,0}$	$mol.m^{-3}$	Initial concentration of active enzyme
$C_{E,i}$	$mol.m^{-3}$	Concentration of active enzyme at the outlet of the i-th reactor
$C_{S,0}$	$mol.m^{-3}$	Initial concentration of substrate
$C_{S,i}$	$mol.m^{-3}$	Concentration of substrate at the outlet of the i-th reactor
Da_i	–	Damköhler number associated with the i-th reactor $((V_i.k_{v,0}.C_{E,0})/(Q.C_{S,0}))$
Da_{min}	–	Minimum value of the overall Damköhler number
Da_{tot}	–	Overall Damköhler number $\left(\sum_{j=1}^{N} Da_j\right)$
E_d	$J.mol^{-1}$	Activation energy of the step of deactivation of the enzyme
E_m	$J.mol^{-1}$	Standard enthalpy change of the step of binding of substrate to the enzyme
E_v	$J.mol^{-1}$	Activation energy of the step of enzymatic transformation of substrate
i	–	Integer variable
j	–	Dummy integer variable
k	–	Dummy integer variable
$k_{d,i}$	s^{-1}	Kinetic constant associated with the deactivation of enzyme in the i-th reactor $(k_{d,0}.\exp\{-E_d/(R.T_i)\})$
$k_{d,0}$	s^{-1}	Preexponential factor of the kinetic constant associated with the deactivation of the enzyme
$K_{m,i}$	$mol.m^{-3}$	Equilibrium constant associated with the binding of substrate to the enzyme in the i-th reactor, $(K_{m,0}.\exp\{-E_m/(R.T_i)\})$
$K_{m,0}$	$mol.m^{-3}$	Preexponential factor of the Michaelis-Menten constant associated with the binding of substrate to the enzyme
$k_{v,i}$	s^{-1}	Kinetic constant associated with the transformation of the substrate by the enzyme in the i-th reactor $(k_{v,0}.\exp\{-E_v/(R.T_i)\})$
$k_{v,0}$	s^{-1}	Preexponential factor of the kinetic constant associated with the transformation of the substrate by the enzyme
N	–	Number of reactors in the series
Q	$m^3.s^{-1}$	Volumetric flow rate of reacting liquid through the reactor network
R	$J.K^{-1}.mol^{-1}$	Ideal gas constant
T_i	K	Absolute temperature at the outlet of the i-th reactor
T_0	K	Initial absolute temperature
V_i	m^3	Volume of the i-th reactor
v_{max}	$mol.m^{-3}.s^{-1}$	Maximum rate of reaction under saturation conditions of substrate
x_i	–	Normalized concentration of substrate $(C_{S,i}/C_{S,0})$
$x_{i,opt}$	–	Optimum value of the normalized concentration of substrate
y_i	–	Dimensionless temperature $(\exp\{-T_0/T_i\})$
$y_{i,opt}$	–	Optimum value of the dimensionless temperature

Greek symbols

α	–	Dimensionless preexponential factor associated with the Michaelis-Menten constant $(K_{m,0}/C_{S,0})$
β	–	Dimensionless activation energy of the step of enzymatic transformation of substrate $(E_v/R.T_0))$
γ	–	Dimensionless standard enthalpy change of the step of binding of substrate to the enzyme $(E_m/(R.T_0))$
δ	–	Dimensionless activation energy of the step of deactivation of the enzyme $(E_d/(R.T_0))$
η	–	Dimensionless deactivation preexponential factor $((k_{d,0}.C_{S,0})/(k_{v,0}.C_{E,0}))$

1 Introduction

Continuous stirred tank reactors (CSTR's) have been used to perform biochemical reactions of industrial interest because they are easy to model and control. Furthermore, their operation is economically feasible provided that (i) large throughput feedstocks are handled, (ii) the reaction products are subject to narrow market specifications, (iii) the cost of enzyme makeup is not high (which usually implies that the level of purity of the enzyme employed with respect to other inert species is not critical for efficient operation), and (iv) the residual enzymatic activity in the effluent stream can be easily destroyed via, e.g., thermal treatment.

Theoretical reasonings underlying the design of a series of CSTR's performing chemical reactions which obey power-law [1, 2] and Michaelis-Menten like rate equations [3–8] have been derived previously. The latter analyses all assume a constant activity of the enzyme along the reactor network and throughout time. Unlike most organic and inorganic reactions effected by homogeneous catalysis, however, the catalyst in enzyme-catalyzed biochemical reactions is often subject to thermal deactivation [9], and this fact must be taken into account in the design of actual reactor networks.

It is the purpose of this report to obtain the optimum temperature and concentration of substrate in each reactor of a series of CSTR's performing an enzyme-catalyzed reaction which obeys Michaelis-Menten kinetics coupled with first order deactivation of enzyme under the assumption that such optimum path gives the minimum overall reactor volume for a given final conversion of substrate.

2 Theory

The problem of interest here is to find the minimum overall reactor volume when a nonisothermal cascade of N CSTR's is employed to bring about an enzyme-catalyzed reaction in the presence of enzyme deactivation.

The steady-state mass balance to enzyme undergoing first order deactivation in a series of CSTR's with a constant rate of addition of fresh enzyme to the first reactor (in order to compensate for the loss of enzyme as a part of the effluent stream from the last reactor in the series) may be written as:

$$Q\,C_{E,i-1} = V_i\,k_{d,i}\,C_{E,i} + Q\,C_{E,i}, \quad i = 1, 2, \ldots, N\ , \qquad (1)$$

where Q is the volumetric flow rate of fluid, V is the reactor volume, k_d is the deactivation constant, C_E is the concentration of active enzyme, and subscript i denotes the i-th reactor in the cascade. Solution of Eq. (1) with respect to $C_{E,i}$ coupled with Arrhenius law, one obtains:

$$C_{E,i} = \frac{C_{E,i-1}}{1 + \frac{V_i}{Q}k_{d,0}\exp\left\{-\frac{E_d}{RT_i}\right\}} \quad i = 1, 2, \ldots, N\ , \qquad (2)$$

where $k_{d,0}$ is the preexponential factor and E_d is the activation energy associated with k_d, T is the absolute temperature, and R is the ideal gas constant. Application of Eq. (2) from $i = 1$ to $i = N$ finally gives:

$$\frac{C_{E,i}}{C_{E,0}} = \frac{1}{\prod_{j=1}^{i}(1 + \eta\,Da_j\,y_j^{\delta})}\ , \qquad (3)$$

where the dimensionless volume (or Damköhler number), Da_i, dimensionless temperature, y_i, dimensionless activation energy, δ, and dimensionless deactivation preexponential factor, η, are defined as $V_i.k_{v,0}.C_{E,0}/(Q.C_{S,0})$, $\exp\{-T_0/T_i\}$, $E_d/(R.T_0)$, and $k_{d,0}.C_{S,0}/(k_{v,0}.C_{E,0})$, respectively, and where C_S denotes the concentration of substrate ($k_{v,0}$ will be defined below).

The steady-state mass balance to substrate undergoing consumption according to the Michaelis-Menten rate expression in a series of CSTR's may be written as:

$$Q\,C_{S,i-1} = V_i\frac{k_{v,i}\,C_{E,i}\,C_{S,i}}{K_{m,i} + C_{S,i}} + Q\,C_{S,i}\ , \qquad (4)$$

where k_v is the catalytic constant and K_m is the Michaelis-Menten constant. The product $k_{v,i}\,C_{E,i}$ is often referred to as the maximum rate of reaction under saturation conditions of substrate, and is commonly denoted as $v_{\max}$. Use of Arrhenius law in Eq. (4), one gets:

$$Q\,C_{S,i-1} = V_i\frac{k_{v,0}\exp\left\{-\frac{E_v}{RT_i}\right\}C_{E,i}\,C_{S,i}}{K_{m,0}\exp\left\{-\frac{E_m}{RT_i}\right\} + C_{S,i}} + Q\,C_{S,i}\ , \qquad (5)$$

where $k_{v,0}$ and $K_{m,0}$ are the preexponential factors associated with k_v and K_m, respectively, E_v is the activation energy associated with k_v, and E_m is the standard enthalpy of reaction associated with K_m. Combining Eq. (3) with Eq. (5) and algebraically rearranging the result, one obtains:

$$x_{i-1} - x_i = \frac{Da_i\,x_i\,y_i^{\beta}}{(\alpha\,y_i^{\gamma} + x_i)\prod_{j=1}^{i}(1 + \eta\,Da_j\,y_j^{\delta})}\ , \qquad (6)$$

where the dimensionless substrate concentration, x_i, dimensionless activation energy, β, dimensionless standard enthalpy change, γ, and dimensionless preexponential factor, α, are defined as $C_{S,i}/C_{S,0}$, $E_v/(R.T_0)$, $E_m/(R.T_0)$, and $K_{m,0}/C_{S,0}$, respectively.

Solving Eq. (6) with respect to Da_i for a generic i, and applying the obtained recurrence relation for Da_j with $1 \leq j < i$ in a way similar to that previously employed by

Malcata [10], one obtains after some manipulation

$$Da_i = \frac{\dfrac{(x_{i-1} - x_i)(\alpha y_i^{\gamma} + x_i)}{y_i^{\beta} x_i}}{1 - \eta \sum_{j=1}^{i} \left(y_j^{\delta} \dfrac{(x_{j-1} - x_j)(\alpha y_j^{\gamma} + x_j)}{y_j^{\beta} x_j} \right)} . \tag{7}$$

The intermediate concentrations of substrate and temperatures which lead to the minimum value for the overall reactor dimensionless volume, Da_{tot}, may then be obtained from the following relationships:

$$\frac{\partial Da_{tot}}{\partial x_i} \equiv \left\{ \frac{\partial \left(\sum_{j=1}^{N} Da_j \{x_1, x_2, \ldots, x_j, y_1, y_2, \ldots, y_j\} \right)}{\partial x_i} \right\}_{x_1, x_2, \ldots, x_{i-1}, x_{i+1}, \ldots, x_N, y_1, y_2, \ldots, y_{i-1}, y_i, y_{i+1}, \ldots, y_N} = 0$$

with $i = 1, 2, \ldots, N-1$, (8)

and

$$\frac{\partial Da_{tot}}{\partial y_i} \equiv \left\{ \frac{\partial \left(\sum_{j=1}^{N} Da_j \{x_1, x_2, \ldots, x_j, y_1, y_2, \ldots, y_j\} \right)}{\partial y_i} \right\}_{x_1, x_2, \ldots, x_{i-1}, x_i, x_{i+1}, \ldots, x_N, y_1, y_2, \ldots, y_{i-1}, y_{i+1}, \ldots, y_N} = 0$$

with $i = 1, 2, \ldots, N-1$, (9)

respectively. Combination of Eq. (8) with Eq. (7) yields, after rearrangement:

$$-\frac{y_i^{-\beta}\left(1 + \alpha y_i^{\gamma} \dfrac{x_{i-1}}{x_i^2}\right)}{1 - \eta \sum_{j=1}^{i} \left(\dfrac{(x_{j-1} - x_j)(\alpha y_j^{\gamma} + x_j)}{x_j} y_j^{(\delta-\beta)} \right)} \left(1 + \frac{\eta \dfrac{(x_{i-1} - x_i)(\alpha y_i^{\gamma} + x_i)}{x_i} y_i^{(\delta-\beta)}}{1 - \eta \sum_{j=1}^{i} \left(\dfrac{(x_{j-1} - x_j)(\alpha y_j^{\gamma} + x_j)}{x_j} y_j^{(\delta-\beta)} \right)} \right)$$

$$+ \frac{\dfrac{\alpha y_{i+1}^{\gamma} + x_{i+1}}{x_{i+1} y_{i+1}^{\beta}} \left(1 - \eta \left(\sum_{j=1}^{i} \left(\dfrac{(x_{j-1} - x_j)(\alpha y_j^{\gamma} + x_j)}{x_j} y_j^{(\delta-\beta)} \right) + (x_i - x_{i+1}) \left(1 + \dfrac{\alpha y_i^{\gamma} x_{i-1}}{x_i^2} \right) y_j^{(\delta-\beta)} \right) \right)}{\left(1 - \eta \sum_{j=1}^{i+1} \left(\dfrac{(x_{j-1} - x_j)(\alpha y_j^{\gamma} + x_j)}{x_j} y_j^{(\delta-\beta)} \right) \right)^2}$$

$$- \sum_{k=2}^{N-i} \frac{\eta \left(y_i^{(\delta-\beta)} \dfrac{x_i^2 + \alpha x_{i-1} y_i^{\gamma}}{x_i^2} - y_{i+1}^{(\delta-\beta)} \dfrac{x_{i+1} + \alpha y_{i+1}^{\gamma}}{x_{i+1}} \right) (x_{i+k-1} - x_{i+k})(\alpha y_{i+k}^{\gamma} + x_{i+k})}{x_{i+k} y_{i+k}^{\beta} \left(1 - \eta \sum_{j=1}^{i+k} \left(\dfrac{(x_{j-1} - x_j)(\alpha y_j^{\gamma} + x_j)}{x_j} y_j^{(\delta-\beta)} \right) \right)^2} = 0 \quad \text{with } i = 1, 2, \ldots, N-1. \tag{10}$$

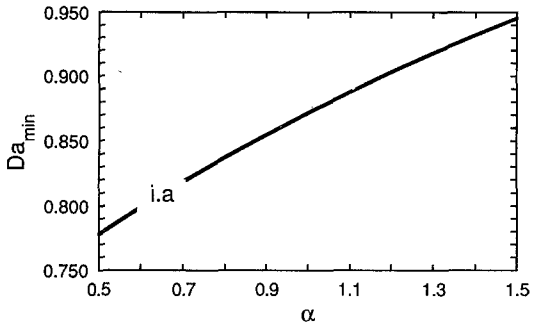
A similar combination of Eq. (9) with Eq. (7) gives, after rearrangement:

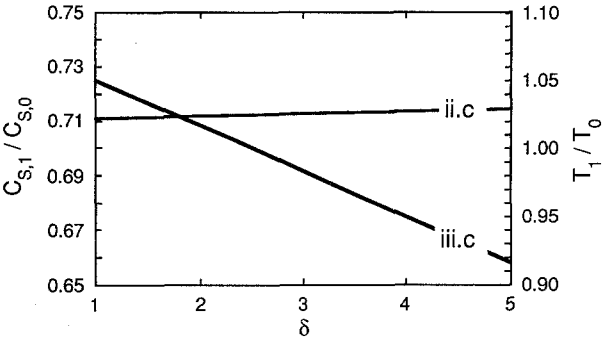
$$y_i^{-(\beta+1)} \left(\frac{x_{i-1}}{x_i} - 1 \right) \frac{\left(\begin{array}{l} \alpha(\gamma - \beta) y_i^{\gamma} - \beta x_i - \eta(\alpha y_i^{\gamma}(\gamma - \beta) - \beta x_i) \left(\sum_{j=1}^{i} \dfrac{(x_{j-1} - x_j)(\alpha y_j^{\gamma} + x_j)}{x_j} y_j^{(\delta-\beta)} \right) + \ldots \\ \ldots \eta y_i^{\delta} \left(\dfrac{x_{i-1}}{x_i} - 1 \right) \left(\alpha(\delta + \gamma - \beta) y_i^{(\gamma-\beta)} (\alpha y_i^{\gamma} + x_i) + (\delta - \beta) x_i y_i^{-\beta} (\alpha y_i^{\gamma} + x_i) \right) \end{array} \right)}{\left(1 - \eta \sum_{j=1}^{i} \left(\dfrac{(x_{j-1} - x_j)(\alpha y_j^{\gamma} + x_j)}{x_j} y_j^{(\delta-\beta)} \right) \right)^2}$$

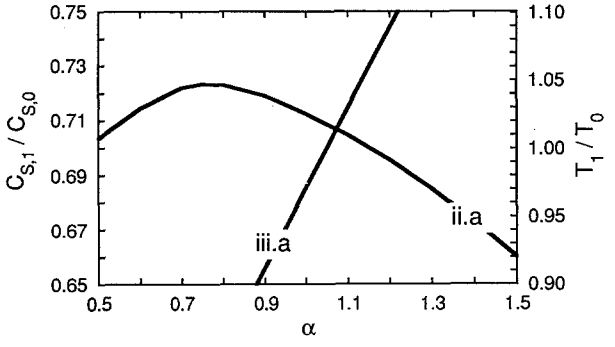
$$+ \sum_{k=1}^{N-i} \frac{\eta y_i^{(\delta-\beta-1)} \dfrac{(x_{i-1} - x_i)(x_{i+k-1} - x_{i+k})(\alpha y_{i+k}^{\gamma} + x_{i+k})}{x_i x_{i+k} y_{i+k}^{\beta}} (\alpha(\gamma + \delta - \beta) y_i^{\gamma} + x_i(\delta - \beta))}{\left(1 - \eta \sum_{j=1}^{i+k} \left(\dfrac{(x_{j-1} - x_j)(\alpha y_j^{\gamma} + x_j)}{x_j} y_j^{(\delta-\beta)} \right) \right)^2} = 0 \quad \text{with } i = 1, 2, \ldots, N-1. \tag{11}$$

The above set of (2N–2) independent equations in (N–1) intermediate concentrations and (N–1) intermediate temperatures can be solved for x_i and y_i by a trial-and-error method. In the particular case of a series of 2 CSTR's, the results are plotted in Fig. 1 for various reasonable values of α, β, γ, δ, and η.

If the rate of deactivation of the enzyme is negligible compared with the overall rate of the enzyme-catalyzed reaction (i.e., when η tends to zero), Eqs. (10) and (11)


Da_min
α
i.a


C_S,1 / C_S,0
T_1 / T_0
δ
ii.c
iii.c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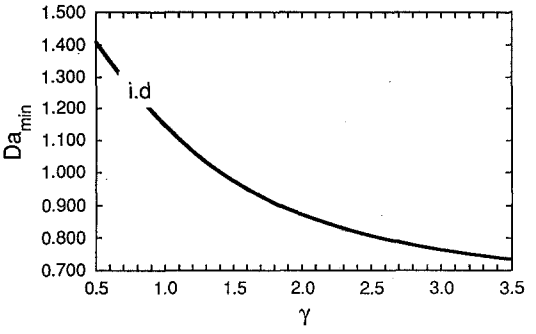
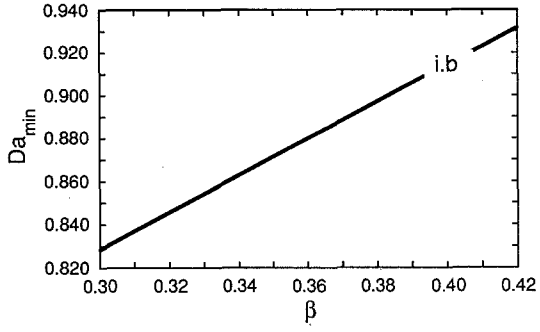
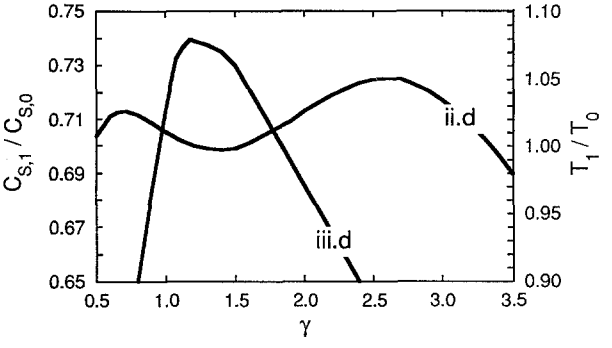
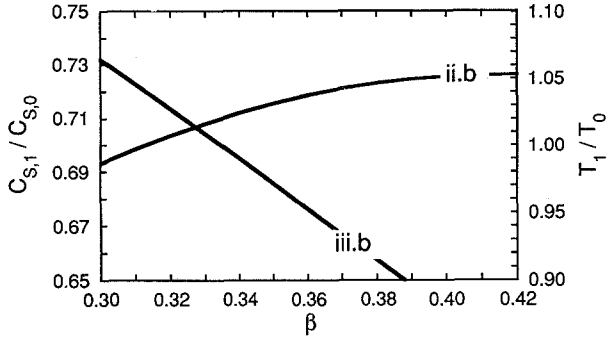
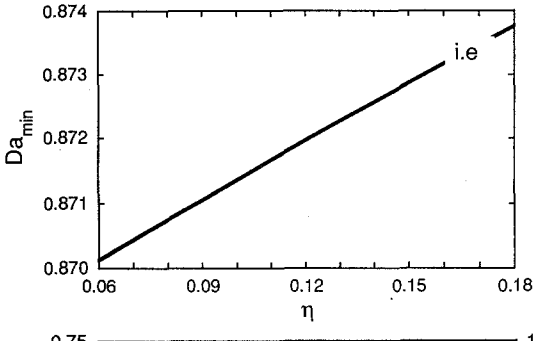
T_1 / T_0
α
ii.a
iii.a

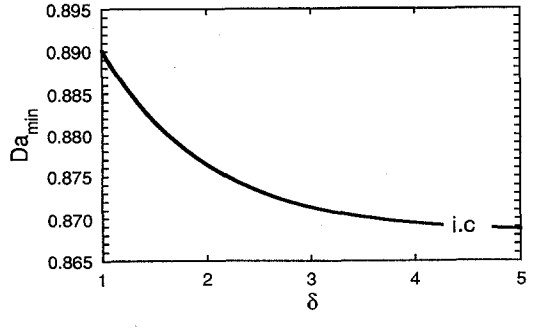

Da_min
γ
i.d

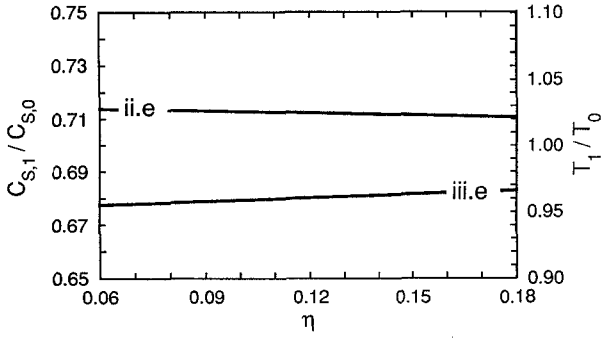

Da_min
β
i.b


C_S,1 / C_S,0
T_1 / T_0
γ
ii.d
iii.d


C_S,1 / C_S,0
T_1 / T_0
β
ii.b
iii.b


Da_min
η
i.e


Da_min
δ
i.c


C_S,1 / C_S,0
T_1 / T_0
η
ii.e
iii.e

reduce to:

$$\frac{\alpha y_{i+1}^{\gamma} + x_{i+1}}{x_{i+1} y_{i+1}^{\beta}} - y_i^{-\beta}\left(1 + \alpha y_i^{\gamma} \frac{x_{i-1}}{x_i^2}\right) = 0 \tag{12}$$

and

$$y_i^{-(\beta+1)}\left(\frac{x_{i-1}}{x_i} - 1\right)(\alpha(\gamma - \beta) y_i^{\gamma} - \beta x_i) = 0 \tag{13}$$

respectively. Equations (12) and (13) can be manipulated to give:

$$x_i = \sqrt{\frac{\alpha x_{i-1} x_{i+1} y_i^{\gamma}\left(\frac{y_{i+1}}{y_i}\right)^{\beta}}{\alpha y_{i+1}^{\gamma} + x_{i+1}\left(1 - \left(\frac{y_{i+1}}{y_i}\right)^{\beta}\right)}} \tag{14}$$

and

$$y_i = \left(\frac{\beta x_i}{\alpha(\gamma - \beta)}\right)^{1/\gamma} \tag{15}$$

respectively. Combining Eqs. (14) and (15), one finally gets

$$\frac{x_i}{x_{i+1}} = \left(1 + \frac{\left(\frac{x_{i-1}}{x_i}\right) - 1}{\left(\frac{\gamma}{\beta}\right)}\right)^{\left(\frac{\gamma}{\beta}\right)} \tag{16}$$

In the absence of deactivation, a local optimum for the temperature exists if (i) K_m increases more rapidly with increasing temperature than does k_v and (ii) if K_m is sufficiently large. The former condition is equivalent to saying that $E_m > E_v$, or, equivalently, $\gamma > \beta$. The latter condition implies that the dimensionless preexponential factor associated with the Michaelis-Menten constant is such that $\alpha > \beta.x_i/(\gamma - \beta)$ (because $0 < y_i < 1$ for all reactors); since $0 < x_i < 1$, a conservative constraint reads $\alpha > \beta/(\gamma - \beta)$. The variation of the ratio of two consecutive optimal concentrations as a function of the previous ratio of consecutive concentrations is plotted in Fig. 2 for several values of parameter γ/β.

When $\beta = \gamma = 0$, Eq. (14) becomes:

$$x_i = \sqrt{x_{i-1} x_{i+1}}\ , \tag{17}$$

which is the result that would also have been obtained if the system were operated under isothermal conditions

Fig. 1. Plots of (i) the minimum Damköhler number, Da_{min}, (ii) the normalized intermediate substrate concentration, $C_{s,1}/C_{s,0}$, and (iii) normalized intermediate temperature, T_1/T_0, versus (a) α (with $\beta = 0.35$, $\gamma = 2$, $\delta = 3$, and $\eta = 0.1$), (b) β (with $\alpha = 1$, $\gamma = 2$, $\delta = 3$, and $\eta = 0.1$), (c) δ (with $\alpha = 1$, $\beta = 0.35$, $\gamma = 2$, and $\eta = 0.1$), (d) γ (with $\alpha = 1$, $\beta = 0.35$, $\delta = 3$, and $\eta = 0.1$), and (e) η (with $\alpha = 1$, $\beta = 0.35$, $\delta = 3$, and $\gamma = 2$), under the assumption that $T_2 = 300$ K and $x_2 = 0.5$

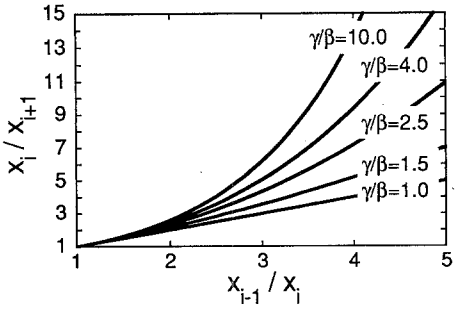


Fig. 2. Plot of the ratio of consecutive normalized concentrations, x_i/x_{i+1}, versus the previous ratio counterpart, x_{i-1}/x_i, for several values of parameter γ/β

[3]. This case corresponds to $x_i/x_{i+1} = x_{i-1}/x_i$, which is the equation of the diagonal in Fig. 2.

3 Discussion and conclusions

It should be noted that although parameters α, β, δ, and η can take only positive values, because activation energies and preexponential factors are always positive, γ is not generally constrained because the binding of substrate to enzyme may be either an endothermic or an exothermic process.

Although Eqs. (10)–(11) correspond to the necessary conditions associated with the minimum overall reactor volume, one or more of the values $x_{i,opt}$ and $y_{i,opt}$ thereby calculated can violate the physical constraints $1 \geq x_{i,opt} \geq x_{i+1,opt}$ and $0 < y_{i,opt} < 1$ for integer values of i comprised between 0 and N. In these situations, there is no local optimum, and the global optimum lies on a temperature constraint, e.g., the minimum or maximum temperature for which operation of the reacting mixture is feasible from hydrodynamic or mechanical points of view. It might also be argued that an exhaustive search pattern for the values of x_i and y_i which minimize Da_{tot} as obtained from Eq. (7) might lead to faster results than use of Eqs. (10)–(11). However, it should be emphasized that as the number of reactors in the series increases, the number of similar calculations using the exhaustive approach increases with n^{2N}, where n is the number of search intervals, and so does the CPU time required. In the general case, the system of $2N$–2 equations denoted as Eqs. (10)–(11) can be solved by an iterative procedure starting with the much simpler solution for $\eta = 0$, i.e., Eqs. (15)–(16).

In the computation of the optimal intermediate concentrations and temperatures, special care should be exercised because, as pointed out elsewhere [10], there is a minimum concentration of substrate at the outlet of each reactor. This observation is due to the existence of two competing processes. Longer residence times lead to larger amounts of substrate transformed per unit of active

enzyme, but longer residence times also lead to a larger extent of deactivation of the enzyme.

In the absence of deactivation, γ must be greater than β so that Eq. (15) is physically consistent; such condition leads to values of the ratio γ/β always above unity. When $\gamma = \beta$, this corresponds to having the system operating under isothermal conditions, in which situation the plot of x_i/x_{i+1} versus x_{i-1}/x_i coincides with the main diagonal in Fig. 2. In this case the optimal intermediate concentration of substrate in every series of two consecutive stirred reactors is equal to the geometric mean of the substrate concentration of the inlet to the first reactor and the substrate concentration of the outlet of the second reactor. In the non-isothermal situations (i.e., $\gamma/\beta > 1$), x_i/x_{i+1} is always above x_{i-1}/x_i; hence the corresponding curves in Fig. 2 are always located above the main diagonal (the deviation with respect to the main diagonal actually increases with increasing γ/β) and x_i is always above $(x_{i-1} . x_{i+1})^{1/2}$.

The ranges selected for the plots denoted as Fig. 1 were those associated with physically reasonable values, i.e., temperatures between ca. 0 and ca. 60 °C, and intermediate concentrations between 0.65 and 0.75, for an initial temperature of 27 °C and an initial normalized concentration of unity. Inspection of Fig. 1.i. indicates that Da_{min} increases with increasing α, β, and η, whereas this behavior is reversed for increasing values of δ and γ; in the former three situations the variation has a linear trend, whereas in the latter two situations the variation has a decreasing hyperbolic trend. With respect to the normalized intermediate concentration, one concludes that it goes through a local maximum at $\alpha \sim 0.7$ (see Fig. 1.ii.a) and through two local maxima located at $\gamma \sim 0.75$ and $\gamma \sim 2.5$ (see Fig. 1.ii.d), whereas in the remaining situations it monotonically increases (see Fig. 1.ii.b and Fig. 1.ii.c) or decreases (see Fig. 1.ii.e). With respect to the normalized intermediate absolute temperature, one concludes that it goes through a local maximum at $\gamma \sim 1.25$ (see Fig. 1.iii.d., whereas in the remaining situations it monotonically increases (see Fig. 1.iii.a. and Fig. 1.iii.e.) or decreases (see Fig. 1.iii.b. and Fig. 1.iii.c.). In general, the variation of Da_{min} with every parameter is much less sensitive to the size of the increment used in a typical exhaustive search than is the variation of C_1/C_0 and T_1/T_0 versus the same parameter. It can also be concluded that the variation in the optimal operating temperature is much sharper than the variation in the optimal intermediate concentration for the same varying parameter. Although the optimal intermediate concentration is always comprised between the inlet and outlet concentrations to the first and from the second reactor, respectively, the same does not apply to the intermediate temperature, which may lead to heating or cooling with refrigeration requirements. As expected, when η tends to zero, the effect of δ on the conclusions becomes also negligible, as apparent from Eq. (7).

The analysis developed above proves that the extra degree of freedom arising from the introduction of temperature as a manipulated variable leads to optimal concentration profiles along the cascade of CSTR's which are substantially different from those which would have been obtained if isothermal operation were assumed throughout. Hence it might be useful in the predesign steps of biochemical reactors.

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